CENTERS FOR INNOVATION IN MEMBRANE PROTEIN PRODUCTION

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Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATIONS:
National Institutes of Health (NIH)
(http://www.nih.gov)

THIS RFA IS DEVELOPED AS A ROADMAP INITIATIVE. ALL NIH INSTITUTES AND CENTERS PARTICIPATE IN ROADMAP INITIATIVES.

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER(S): 93.859

LETTER OF INTENT RECEIPT DATE: February 5, 2004
APPLICATION RECEIPT DATE: March 11, 2004

THIS RFA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS RFA

This Request for Applications (RFA) solicits proposals to establish Centers for Innovation in Membrane Protein Production. The goals of these Centers will be to create enabling technologies and to focus on innovative, high-impact, and multidisciplinary approaches to sample preparation of structurally and functionally intact membrane proteins for structure determination. The collaborative and coordinated effort made

possible by multiple, interdisciplinary investigators associated with research Centers is required to accelerate technological advances in this important area. The goal of the Centers, not possible with other funding mechanisms or previous program announcements, will be the multidisciplinary and non-hypothesis-driven technology development of innovative tools and methods for the expression, solubilization, stabilization, reconstitution, and purification of membrane proteins. The Centers will disseminate their results, methods, and materials in a timely manner. They will also track state-of-the-art developments in membrane protein production and structure determination as guides in the selection of appropriate subprojects, cores, approaches, and targets. It is expected that the activities of the Centers for Innovation in Membrane Protein Production will complement the activities of investigator-initiated research, as supported by the R01, R21, and P01 mechanisms, and the goals of the NIGMS Protein Structure Initiative research centers. Because no single institution may have the variety of expertise required for membrane protein preparation and characterization, Centers involving multiple, cooperating institutions bringing together innovative combinations of scientific disciplines will be encouraged.

RESEARCH OBJECTIVES

Membrane proteins play a crucial role in many cellular and physiological processes. They are essential mediators of material and information transfer between cells and their environment, between compartments within cells, and between compartments comprising the organ systems. Functionally normal membrane proteins are vital to health, and specific defects are associated with many known disease states. Membrane proteins are the targets of a large number of pharmacologically and toxicologically active substances and are responsible, in part, for their uptake, metabolism, and clearance.

The NIH Roadmap process for program initiative prioritization, established by the NIH Director, Dr. Elias Zerhouni (http://nihroadmap.nih.gov), has identified Structural Biology as a major area for additional near-term investment. Determining the structures of membrane proteins is an intermediate- to long-term goal. An increase in the number of known membrane protein structures will contribute to an enhanced understanding of many basic phenomena underlying cellular functions essential to human health. Improved membrane protein preparation using novel approaches is an important first step.

The goal of the Centers is the development of innovative, multidisciplinary methods that will yield structurally and functionally intact membrane proteins for subsequent structural studies. Thus far, most membrane protein structures have been solved for proteins that can be obtained from naturally rich sources. However, many of the proteins of greatest human physiological and pharmaceutical relevance are of relatively low abundance. Although membrane proteins may be expressed in recombinant form, there is a need to develop more robust expression systems for membrane proteins. For oligomeric membrane proteins, efficient co-expression of membrane protein subunits and assembly systems are required.

Centers may focus on why certain detergents and/or lipids with novel phase properties are more successful in the solubilization of membrane proteins than others. Studies leading to the chemical synthesis of novel detergents and/or the development of non-detergent methods for solubilizing and stabilizing membrane proteins are encouraged. Other research areas should include efficient methods to characterize the functional state of the expressed and purified membrane proteins as well as their lipid and detergent contents, state of aggregation, physical homogeneity, and sequence microheterogeneity. Protein characterization may include tests of the suitability of purified proteins for structure determination, such as preliminary crystallization trials or NMR analyses, but these activities are not to be major activities funded by the Center grant awards.

The development of innovative, multidisciplinary, and even speculative, approaches to the fractionation and purification of membrane proteins is also highly encouraged. Novel applications of genomic and proteomic approaches and screens that might complement or enhance traditional approaches such as centrifugation, partitioning, precipitation, chromatography, isoelectric focusing, and electrophoresis are requested. Non-traditional approaches such as the use of protein and/or lipid chaperones, conformation-specific antibodies, covalent modification, stabilizing mutations, and structural scaffolds should be proposed to express, solubilize, and purify membrane proteins.

Although the application of the purified membrane protein samples is structure determination, the major focus of each Center should be development of innovative approaches for obtaining membrane proteins that are structurally and functionally intact. It is expected that these Centers will contribute to the solution of many more membrane protein structures over the next five years through collaboration with researchers funded outside the scope of the Centers. These contributions to knowledge of membrane protein structure and membrane-protein association should feed back into an understanding of ways to improve expression, solubilization, stabilization, reconstitution, and purification.

A program announcement on the Structural Biology of Membrane Proteins has been in effect for several years (see: http://www.nigms.nih.gov/funding/pa/membrane.html). This announcement includes research on protein production, crystallization, isotopic labeling, and the solution of membrane protein structures. Thus far, most responsive projects have involved single or relatively small groups of researchers and standard approaches. The Centers will provide opportunities for larger, organized, multidisciplinary and collaborative groups of researchers to attack these problems, and they are expected to use novel and high risk approaches for membrane protein preparation and to facilitate interactions with and among the smaller groups of researchers.

The Protein Structure Initiative (PSI; see: http://www.nigms.nih.gov/psi/) seeks to accelerate the rate of protein structure solution. Some of the PSI centers include limited efforts to determine membrane protein structures, and the PSI program announcements encourage support of technology development for high-throughput approaches to membrane protein structure determination (see: http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-00-006.html). However, based on a workshop evaluating progress of the

PSI research centers, protein production is one of the major rate limiting steps to structure determination, and this is especially true with respect to membrane proteins (see: http://www.nigms.nih.gov/news/reports/protein_production.html). Therefore, there is a need for a separate program initiative that focuses primarily on the coordinated development of innovative and high-risk methods for membrane protein preparation.

MECHANISM OF SUPPORT

This RFA will use NIH P50 Specialized Center Grant award mechanism to promote multidisciplinary research focused on the goal of developing innovative methods for expressing, solubilizing, reconstituting, and purifying membrane proteins in a functional form suitable for structure determination and characterization. Center Grants provide support for innovative subprojects and allow more flexibility to modify research goals when new opportunities arise.

The applicant will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. The anticipated award date is by September 30, 2004.

Groups of investigators interested in the subject area of this RFA, but wishing to mount a project of smaller scope, might find the P01 mechanism more appropriate (see: http://grants.nih.gov/grants/guide/pa-files/PA-01-116.html.

Although not discouraged, this program does not require cost sharing, as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm. However, evidence of institutional commitment and support should be presented.

FUNDS AVAILABLE

The NIH intends to commit approximately $5.0 million in FY2004 to fund at least two new Center grants in response to this RFA. An applicant may request a project period of up to five years and a budget for total direct costs of up to $1.5 million for the first year. Facilities and administrative (F & A) costs on subprojects are not included in this cap. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the ICs provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

ELIGIBLE INSTITUTIONS

You may submit an application if your institution is domestic and has one of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of state and local governments
o Eligible agencies of the Federal government

The majority of the research should be done at domestic institutions, but a Center may include a foreign subproject. Although NIH may not award a grant to an NIH component, an NIH component may be included as a subproject or a scientific collaboration associated with the Center. However, funds are not allocated to intramural NIH investigators and laboratories, unless under extremely rare and exceptional circumstances.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his/her institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

Center Structure:

Subprojects for Methods Development: The principal funded research to be carried out by the Centers will be the technological development of innovative methods for the expression, over-expression, solubilization, stabilization, reconstitution, and purification of membrane proteins. This research should be set out as a series of specific, multidisciplinary subprojects, each focusing on different but complementary and novel approaches. Additional goals of the Centers should be the dissemination of the methods developed and their availability to investigators outside the Center. These subprojects should be headed by an appropriately qualified investigator, who may or may not be the overall Center director and principal investigator (PI). Not all subprojects need to begin in the first year. Some may be phased-in as progress on the initial projects allows. A variety of approaches to each problem should be presented.

Core Research Facilities: The rationale for establishing a Center should be the common scientific objectives of the participants, not the support of a core facility. However, a Center application may request support for scientifically justified facilities, including equipment and support personnel. Plans should be presented for providing core access to all participants in the Center and for making unique Center facilities available to collaborating researchers outside of the Center participants.

Administrative Core: A plan should be presented for the overall administration of the Center and for the prioritization, selection, deletion, and evaluation of subprojects, cores, methods, and approaches. Plans for rapidly adjusting the Center priorities as projects

succeed or fail should also be outlined. Methods and criteria for flexibly evaluating, initiating, and replacing cores and subprojects should be described. The decision making process for disseminating methods and results should be presented. This dissemination should take the form of a database, website, or other appropriate information tools. The PI should indicate how the methods and open-source software developed by the Center will be available to the research community. A plan should be presented for citation of Center support, determining authorship, and resolving other acknowledgement and intellectual property (IP) issues that may arise among participants and collaborators. The PI has responsibility for the overall operation of the Center. Delegated areas of responsibility should be clearly indicated. Plans for any internal or external advisory committees should be specified, but advisory committee members should not be identified or selected until after an award has been made.

Information Sharing: It is expected that Center participants will publish their results in the usual ways. In addition, Centers should include plans to establish databases or websites for the purpose of sharing information, such as experimental protocols, materials, software programs, and results, including negative data that are not generally publishable in great detail. Plans for reducing positive data and outcomes to best practices should also be outlined.

Annual Meeting: All Center participants should meet on at least an annual basis. The meetings may be held at the home institution of the Center's principal investigator, at one of the other participating institutions, or at another location, such as in conjunction with a relevant scientific meeting, or in Bethesda. Travel funds to support this activity should be requested in the budget. NIH staff should be invited to participate in these meetings. Other mechanisms should also be presented to assure regular communication and interaction between Center participants.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

John C. Norvell, Ph.D.
Division of Cell Biology and Biophysics
National Institute of General Medical Sciences
Building 45, Room 2AS.13B, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-0533
FAX: (301) 480-2004
Email: norvellj@nigms.nih.gov

o Direct your questions about peer review issues to:

Helen R. Sunshine, Ph.D.
Office of Scientific Review
National Institute of General Medical Sciences
Building 45, Room 3AN.12F, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-2881
FAX: (301) 480-8506
Email: sunshinh@nigms.nih.gov

o Direct your questions about financial or grants management matters to:

Ms. Grace Olascoaga
Division of Extramural Activities
National Institute of General Medical Sciences
Building 45, Room 2AN.32E, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-5520
FAX: (301) 480-2554
Email: olascoag@nigms.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

o Descriptive title of the proposed research
o Name, address, and telephone number of the Principal Investigator
o Names of other key personnel
o Participating institutions
o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

John C. Norvell, Ph.D.
Division of Cell Biology and Biophysics
National Institute of General Medical Sciences
Building 45, Room 2AS.13B, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-0533
FAX: (301) 480-2004

Email: norvellj@nigms.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo,
Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SUPPLEMENTARY INSTRUCTIONS:

The Center should support an integrated, coordinated program, with various interdependent subprojects. The subprojects and cores must be fully described and justified. Collaborations and consortia are encouraged. In such collaborations, the respective contributions should be well integrated into the design of the application. The application should have a face page; abstract; key personnel listing; consolidated budget; subproject and core budgets; biographical sketches; institutional support, resources and facilities; project summary; subproject and core descriptions; plans for administrative management; plans for project management with annual milestones and evaluations; plans for sharing results and materials; plans for handling intellectual property issues; description of any consortium arrangements; and letters of collaboration. The project summary section should define the overall scope and objectives of the Center.

The page limit for the research plan (including specific aims, background and significance, preliminary studies, and research design and methods) is increased to 60 pages total.

The budget should be no greater than $1.5 million direct costs for the first year, with annual cost-of-living increases in subsequent years. It should be fully justified and should include funds for attending the annual meeting.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In

addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and five signed, photocopies, in one package to:

Center For Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes. While the investigator may still benefit from the previous review, the RFA application is not to state explicitly how.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIGMS. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration. Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened according to NIH procedures in accordance with the review criteria stated below.

As part of the initial merit review, all applications will:

o Receive a written critique
o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
o Receive a second level review by the appropriate Advisory Council or Board.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The goal of the P50 Centers for Innovation in Membrane Protein Production is to promote multidisciplinary and interdisciplinary approaches to develop innovative methods and technologies to express, solubilize, reconstitute, and purify membrane proteins. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

o Significance
o Approach
o Innovation
o Investigator
o Environment
o Additional Review Criteria (see below)

The scientific review group will address and consider each of these criteria in assigning the application's overall score, weighting them as appropriate for each application. The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative or hypothesis driven but is essential to move a field forward. If the P50 Center grant application includes distinct subprojects and scientific cores, the scientific merit of each will be assessed, based on its merit, its potential contribution to the success of the overall project, and its interactions with other subprojects, the cores, collaborators, and the scientific community. However, separate priority scores will not be assigned for subprojects and cores. The overall priority score assigned to the Center proposal will reflect the reviewers' enthusiasm for the Center as a whole, taking into account their levels of enthusiasm for only those projects and cores, which they recommend for funding. Projects and cores which are seriously flawed and not recommended for inclusion in the Center will be specifically noted in the text of the summary statement.

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? Are a variety of strategies presented?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies? Are the approaches multidisciplinary and high impact?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Do the principal investigator and subproject investigators have the managerial experience and leadership skills required? Is the principal investigator committed to the center, its goals, and projects?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features and resources of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

Interactions and Interdisciplinarity: Degree to which the subprojects interact with each other and with the cores to create a Center, which is more than the sum of the parts. Degree to which to the goal of promoting interdisciplinary interactions among scientists is achieved.

Plans for Evaluating and Prioritizing Subprojects and scientific cores: Adequacy of plans for selecting and evaluating a variety of subprojects and scientific cores for membrane protein preparation and purification, for tracking new ideas and developments, and for modifying, adding, or deleting subprojects and cores because of these new developments.

Plans for Making Center Facilities Available: Adequacy of plans to make unique Center facilities, results, materials, and methods available to collaborative researchers and to enhance collaborations.

Plans for the Overall Administration: Adequacy of plans for any internal or external advisory committees, for annual and strategic planning meetings, for assuring

communication, interaction, and synergy among Center participants and the scientific community, and for handling intellectual property issues.

Plans for Data Sharing: Adequacy of plans for sharing of Center discoveries and data via databases, websites, distribution of software, and other means of dissemination beyond the usual publication of results.

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below.)

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below.)

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL REVIEW CONSIDERATIONS

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: February 5, 2004
Application Receipt Date: March 11, 2004
Peer Review Date: June-August, 2004
Council Review: September 2004
Earliest Anticipated Start Date: September 30, 2004

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit (as determined by peer review)
o Availability of funds
o Programmatic priorities.

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that

applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

SHARING RESEARCH DATA: Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible. http://grants.nih.gov/grants/policy/data_sharing Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule.

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS: The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving

human subjects that is available at
http://grants.nih.gov/grants/funding/children/children.htm

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov). It is the responsibility of the applicant to provide, in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION: The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so

by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.healthypeople.gov/.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284)and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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Department of Health
and Human Services

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892